Carrier-mediated fructose uptake significantly contributes to carbohydrate metabolism in human skeletal muscle

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To determine whether fructose can be utilized as a metabolic substrate for skeletal muscle in man, we investigated its incorporation into glycogen, its oxidation and lactate production in isolated human skeletal muscle. Rates of fructose oxidation and incorporation into glycogen increased in the presence of increasing fructose concentrations (0.1–1.0 mM). Lactate production increased 3-fold when extracellular fructose was increased from 0.1 to 0.5 mM. Cytochalasin B, a competitive inhibitor of hexose transport mediated by the GLUT1 and GLUT4 facilitative glucose transporters, completely inhibited insulin-stimulated glucose incorporation into glycogen and glucose oxidation ($P < 0.01$), but did not alter fructose incorporation into glycogen or fructose oxidation. Insulin (1000 μ-units/ml) increased glucose incorporation into glycogen 2.7-fold and glucose oxidation 2.3-fold, whereas no effect on fructose incorporation into glycogen or fructose oxidation was noted. A physiological concentration of glucose (5 mM) decreased the rate of 0.5 mM fructose incorporation into glycogen by 60% ($P < 0.001$), whereas fructose oxidation was not altered in the presence of 5 mM glucose. Irrespective of fructose concentration, the majority of fructose taken up underwent non-oxidative metabolism. Lactate production accounted for approx. 80% of the fructose metabolism in the basal state and approx. 70% in the insulin (1000 μ-units/ml)-stimulated state. In the presence of 5 mM glucose, physiological concentrations of fructose could account for ~ 10–30% of hexose (glucose + fructose) incorporation into glycogen under non-insulin-stimulated conditions. In conclusion, fructose appears to be transported into human skeletal muscle via a carrier-mediated system that does not involve GLUT4 or GLUT1. Furthermore, under physiological conditions, fructose can significantly contribute to carbohydrate metabolism in human skeletal muscle.

INTRODUCTION

The fraction of total calories derived from fructose, a naturally occurring ketohexose (α-D-fructofuranose), is increasing in Western diets [1]. The average daily intake of fructose in the United States has been estimated to amount to 7–9% of total energy intake [1]. In humans, fructose is metabolized mainly in the liver and kidney to glucose, glycogen, lactate, triacylglycerols and CO_2 [2]. Ingestion of fructose has been demonstrated to result in a relatively small increase in blood glucose compared with glucose ingestion [3]. This low hyperglycaemic effect of fructose has been explained by the fact that it has a very small effect on overall glucose appearance and a sparing effect on glucose metabolism [4].

When compared with glucose, the hexose most predominantly utilized by skeletal muscle, fructose appears to be more readily incorporated into glycogen [5]. After an intravenous infusion, fructose has been demonstrated to disappear from the bloodstream more rapidly than glucose, and leads to a greater production of lactate [5]. In man, skeletal-muscle glycogen content has been reported to increase in response to fructose infusion [6,7]. The observed increase in muscle glycogen has been reported to occur despite alterations in circulatory levels of glucose [6], and offers indirect evidence that a portion of circulating fructose is converted directly into muscle glycogen. Despite these findings, there remains no direct evidence for fructose utilization in human skeletal muscle under physiological conditions.

The human small-intestine facilitative glucose-transporter protein, GLUT5, has been reported to be easily observed in postnuclear membranes from human small intestine, kidney, heart, skeletal muscle, brain and plasma membrane from adipocytes [8]. Moreover, recent studies have revealed that GLUT5 is specifically localized to the plasma membrane in human skeletal muscle [9,10], and fractionation studies using human adipocytes [8] or human skeletal muscle [10] demonstrate that it is not further recruited to the plasma membrane in response to insulin stimulation. As the biochemical and physiological role ascribed to GLUT5 is that of a high-affinity fructose transporter [11], and as GLUT5 protein is expressed in human skeletal muscle [8,10], there is a need for further characterization of the fructose-transport process in this tissue.

To determine whether fructose can be used directly by muscle as a metabolic substrate, we have employed an *in vitro* technique [12] to assess the uptake and utilization of physiological concentrations of fructose at the cellular level in isolated human skeletal muscle. Furthermore, we have determined the relationship between fructose oxidation, incorporation into glycogen and lactate production in this tissue. Our results are the first to indicate that (1) fructose can indeed be transported into human skeletal muscle via a carrier-mediated system that does not involve GLUT4 or GLUT1 and (2) physiological concentrations of fructose can account for ~ 10–30% of glycogen synthesis in muscle, when both glucose and fructose are present. Thus, under physiological conditions, fructose may play an important role in carbohydrate metabolism in human skeletal muscle.

Abbreviations used: GLUT1, HepG2-cell glucose-transporter protein; GLUT4, insulin-responsive glucose-transporter protein; GLUT5, small-intestine facilitative glucose-transporter protein; KHB, Krebs–Henseleit bicarbonate buffer.

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MATERIALS AND METHODS

Materials

All chemicals, unless specifically stated, were obtained from Sigma (St. Louis, MO, U.S.A.). All radioactive products were from New England Nuclear (Boston, MA, U.S.A.). The insulin (Actrapid) was a product of Novo Nordisk A/S (Copenhagen, Denmark).

Subjects

Fourteen healthy male volunteers (aged 28±1 years; body mass index, 24.2±0.6 kg/m^2) (means±S.E.M.) gave their informed consent to participate in the present study. None were taking any medication or had a family history of metabolic disorders, and all were non-smokers. They had normal serum insulin (7.4±1.2 μ-units/ml; Phadeseph insulin; RIA method; Pharmacia, Uppsala, Sweden) and plasma glucose (4.7±0.2 mM; glucose dehydrogenase method; Merck, Darmstadt, Germany) levels. The study protocol was reviewed and approved by the ethical committee of the Karolinska Institute. All investigations were performed in accordance with the Declaration of Helsinki.

Muscle biopsy procedure

Vastus lateralis skeletal-muscle samples were obtained from the subjects by means of an open-muscle biopsy as previously described [12]. The vastus lateralis muscle is the most frequently utilized human skeletal muscle for biopsy purposes because of its accessibility and lack of major vessels and nerves. The fibre-type composition has recently been demonstrated to be 38% type I, 34% type IIa and 28% type IIb [10]. After surgical excision, the muscle specimens were transported to the laboratory in Krebs–Henseleit bicarbonate buffer [13] (KHB) supplemented with 5 mM Hepes, 2 mM pyruvate and 0.1% BSA (RIA grade).

From the larger specimen, isolated human skeletal-muscle strips (~ 18 mg) were prepared [12], mounted on Plexiglas clamps, and incubated *in vitro* for subsequent assessment of fructose or glucose oxidation, lactate production and the rate of hexose incorporation into glycogen. Immediately after preparation, the muscle strips were incubated (35 °C) for 15 min in sealed flasks containing 2 ml of KHB solution as described above. This initial incubation phase was included to equilibrate the muscle specimen with the incubation environment. Unless specifically stated, the incubation medium was continuously oxygenated with 95% O_2/5% CO_2 throughout each incubation period. In all cases, mannitol was included in the incubation medium to maintain osmolarity (40 mM) in the absence or presence of pyruvate, glucose, 2-deoxyglucose or fructose.

Determination of oxidation of [U-^{14}C]fructose and glycogen synthesis

After the equilibration period, the skeletal-muscle strips were incubated for 2 h in 1.5 ml of KHB solution containing unlabelled fructose, as described in the Table legends, and [U-^{14}C]fructose (0.6 μCi/ml). In some experiments, the muscle strips were incubated in the presence of [U-^{14}C]fructose (0.6 μCi/ml) with the further addition of glucose, 2-deoxyglucose, cytochalasin B, insulin or a combination of the above, in concentrations as indicated in the Tables. During this phase of the incubation procedure, the muscle strips were exposed to the 95% O_2/5% CO_2 for only the first 15 min of every hour. For the experiments where muscle strips were exposed to glucose, 2-deoxyglucose or cytochalasin B, a 30 min pre-exposure to these compounds was included before exposure to [U-^{14}C]fructose. Cytochalasin B is a fungal metabolite which, when bound to the facilitative glucose transporters, inhibits facilitative D-glucose transport [14], but not fructose transport mediated by GLUT5 [11].

After incubation, the muscle specimens were rapidly removed and frozen in liquid nitrogen. The 95% O_2/5% CO_2 gas line was removed, and the liberated $^{14}CO_2$ was collected (1 h; 35 °C) in a hanging centre well situated in the resealed flask [15]. The samples were then processed for total liberated $^{14}CO_2$ as described by Young et al. [15]. The incubated muscle specimens were used to determine glycogen synthesis. Briefly, the skeletal-muscle strips were processed as described by Cuendet et al. [16], glycogen was precipitated [17] and [U-^{14}C]fructose was used to estimate glycogen synthase activity.

Determination of oxidation of [U-^{14}C]glucose and glycogen synthesis

Skeletal-muscle strips were incubated as described above in KHB medium containing unlabelled glucose (concentrations given in the Tables) and [U-^{14}C]glucose (0.3 μCi/ml). After incubation, the muscle specimens were removed, and the liberated $^{14}CO_2$ was collected as described above for the muscles exposed to [U-^{14}C]fructose [15]. The muscle specimens were then processed for the estimation of glycogen synthesis [16,17].

Measurement of lactate production

Incubated skeletal-muscle strips were extracted and neutralized as described previously [18], and lactate levels were assessed fluorimetrically in the tissue extract and the incubation media as described by Gutman and Wahlefeld [19]. Total lactate production was reported as the sum of the tissue lactate plus the lactate released by the muscle into the medium during incubation *in vitro*.

Statistical analysis

Values are reported as means±S.E.M. A one-way analysis of variance was employed to evaluate the statistical significance between the various perturbations. When this revealed statistically significant differences, the Fisher *post-hoc* analysis was used. Student's unpaired *t* test was utilized for statistical comparisons when only two groups of data were assessed.

RESULTS

Fructose oxidation and incorporation into glycogen and lactate production

An increase in the extracellular concentration of fructose from 0.1 to 0.5 mM resulted in an increase in both fructose oxidation and incorporation into glycogen (Table 1). The rate of both these processes was saturated at 0.5 mM fructose, as a further increase in extracellular fructose from 0.5 to 1.0 mM did not further increase glycogen formation (79.0±4.0 and 82.3±8.8 nmol/h per g respectively) or oxidation (8.4±2.8 and 8.8±0.7 nmol/h per g respectively).

Little is known about the capacity of GLUT4 to transport fructose, partly because of the difficulties in obtaining functional expression of human GLUT4 mRNA in *Xenopus* oocytes, a suitable model for the study of the kinetics, and partly because of the substrate specificity of the individual sugar transporters *in vitro*. The presence of 50 μM cytochalasin B, a competitive inhibitor of GLUT1- and GLUT4-mediated hexose transport, had no effect on the rate of fructose oxidation or incorporation into glycogen (Table 1). Furthermore, insulin (1000 μ-units/ml),

Table 1 Effects of cytochalasin B and insulin on fructose oxidation and incorporation into glycogen and lactate production

Isolated human skeletal-muscle stirps were prepared and incubated as described in the Materials and methods section. Values represent means ± S.E.M. for the number of muscle strips indicated in parentheses. Lactate production is calculated as glucose equivalents. N.D., Not determined.

	Fructose incorporation into glycogen (nmol/h per g)	Fructose oxidation (nmol/h per g)	Lactate production (nmol/h per g)
Fructose (0.1 mM)	7.5 ± 2.1 (5)	1.1 ± 0.3 (4)	106 ± 2 (4)
Fructose (0.1 mM) + cytochalasin B (50 μM)	11.2 ± 1.7 (9)	2.5 ± 0.6 (9)	105 ± 3 (3)
Fructose (0.1 mM) + insulin (1000 μ-units/ml)	6.8 ± 1.0 (12)	2.3 ± 0.4 (10)	N.D.
Fructose (0.5 mM)	79.0 ± 4.0 (4)	8.4 ± 2.8 (5)	326 ± 17 (4)
Fructose (0.5 mM) + cytochalasin B (50 μM)	73.2 ± 3.4 (5)	9.2 ± 2.5 (6)	302 ± 25 (3)
Fructose (0.5 mM) + insulin (1000 μ-units/ml)	58.3 ± 5.6 (4)	3.6 ± 0.4 (4)	162 ± 7 (2)

Table 2 Glucose incorporation into glycogen and glucose oxidation in human skeletal-muscle strips

Muscle strips were incubated in the presence of 5 mM glucose and insulin (1000 μ-units/ml) or in the presence of 5 mM glucose, insulin (1000 μ-units/ml) and cytochalasin B (50 μM). The number of muscle strips is given in parentheses. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with value obtained in the presence of glucose (5 mM) only.

	Glucose incorporation into glycogen (nmol/h per g)	Glucose oxidation (nmol/h per g)
Glucose (5 mM)	68.0 ± 7.2 (4)	25.5 ± 3.0 (4)
Glucose (5 mM) + insulin (1000 μ-units/ml)	184.8 ± 28.4 (6)**	58.5 ± 15.6 (5)*
Glucose (5 mM) + insulin (1000 μ-units/ml) + cytochalasin B (50 μM)	28.4 ± 2.8 (8)	19.8 ± 2.7 (6)

Table 3 Effects of glucose on fructose metabolism in human skeletal muscle

Muscle strips were incubated in KHB medium containing either 0.1 or 0.5 mM fructose in the presence or absence or 5 mM glucose. Results are means ± S.E.M. obtained with five to eight muscle strips. $^{***}P < 0.001$ compared with the value obtained in the absence of glucose.

	Fructose incorporation into glycogen (nmol/h per g)		Fructose oxidation (nmol/h per g)	
	−Glucose	+Glucose	−Glucose	+Glucose
Fructose (0.1 mM)	7.5 ± 2.1	6.4 ± 1.1	1.1 ± 0.3	1.7 ± 0.3
Fructose (0.5 mM)	79.0 ± 4.0	31.9 ± 4.7***	8.4 ± 2.8	13.5 ± 3.3

a potent stimulator of GLUT4-mediated hexose transport, did not alter the rate of these processes (Table 1).

Total lactate production in the presence of 0.1 mM fructose amounted to 106 ± 2 nmol/h per g. Increasing the extracellular concentration of fructose to 0.5 mM resulted in a 3-fold increase in lactate production (Table 1). The presence of cytochalasin B did not alter lactate production at either concentration. Insulin at a concentration of 1000 μ-units/ml decreased the lactate production observed in the presence of 0.5 mM fructose. In the presence of 0.5 mM fructose, lactate production was estimated to account for 79 ± 3%, fructose incorporation into glycogen for 19 ± 1% and fructose oxidation for approx. 2% of total metabolism (Table 1). The presence of insulin at a concentration of 1000 μ-units/ml decreased the percentage of lactate production and increased fructose incorporation into glycogen (Table 1).

Glucose oxidation and incorporation into glycogen and lactate production

Insulin (1000 μ-units/ml) induced a 2.7-fold ($P < 0.01$) and 2.3-fold ($P < 0.05$) increase in the basal rate of glucose incorporation into glycogen and glucose oxidation respectively (Table 2). Cytochalasin B completely blocked insulin-induced glucose incorporation into glycogen ($P < 0.001$) and glucose oxidation ($P < 0.01$). The presence of 5 mM glucose resulted in the production of 516 ± 27 nmol of lactate/h per g. In the present investigation, we assessed the three most predominant metabolic pathways of hexose metabolism, lactate production, glycogen formation and oxidation, and found that ~ 96% of glucose metabolism could be accounted for by non-oxidative metabolism and ~ 4% by oxidative metabolism. Insulin (1000 μ-units/ml) increased the relative contribution of oxidative glucose metabolism to 8%.

Effects of glucose and 2-deoxyglucose on fructose metabolism

In order to determine whether or not human skeletal-muscle fructose metabolism interacts with glucose metabolism, we conducted a series of experiments to assess the displacement of fructose by glucose or the glucose analogue, 2-deoxyglucose. Co-addition of physiological concentrations (5.0 mM) of glucose and fructose at a concentration of 0.1 mM did not significantly alter the rate of fructose incorporation into glycogen (Table 3). However, when muscles were incubated in the presence of higher concentrations of fructose (0.5 mM), co-addition of glucose (5.0 mM) inhibited the rate of fructose incorporation into glycogen by 60% ($P < 0.001$). Nevertheless, even in the presence of physiological concentrations of glucose, a 5-fold increase in the medium concentrations of fructose (0.1 to 0.5 mM) resulted in a 4.7-fold increase in fructose incorporation into glycogen.

Table 4 Contribution of fructose to hexose incorporation into glycogen and hexose oxidation in human skeletal muscle

Hexose (glucose + fructose) incorporation into glycogen and hexose oxidation were assessed for human muscle strips exposed to physiological concentrations of glucose (5 mM) and fructose (at 0.1 or 0.5 mM) in the basal or insulin-stimulated (1000 μ-units/ml) state. Results are means ± S.E.M. obtained with four to eight muscle strips.

	Hexose incorporation into glycogen (nmol/h per g)			Hexose oxidation (nmol/h per g)		
	Total	Fructose	Contribution of fructose (%)	Total	Fructose	Contribution of fructose (%)
Fructose (0.1 mM)	71.3 ± 8.7	6.4 ± 1.2	9	25.7 ± 3.7	1.8 ± 0.3	7
Fructose (0.5 mM)	96.8 ± 8.7	31.9 ± 4.7	33	35.2 ± 3.8	11.2 ± 2.9	32
Fructose (0.1 mM) + insulin (1000 μ-units/ml)	230 ± 24	6.8 ± 1.0	3	71.4 ± 14.2	1.7 ± 0.3	2
Fructose (0.5 mM) + insulin (1000 μ-units/ml)	255 ± 24	32.0 ± 4.8	13	80.7 ± 14.2	12.3 ± 3.0	15

Fructose oxidation, assessed at concentrations of 0.1 and 0.5 mM, was not altered by the presence of glucose (5 mM) (Table 3).

In a second set of experiments, skeletal-muscle strips were preincubated in the absence or presence of 30 mM 2-deoxyglucose, and then exposed to 1 mM fructose in the absence or presence of 30 mM 2-deoxyglucose. 2-Deoxyglucose is a glucose analogue which is presumably transported across the muscle cell plasma membrane by GLUT 4 and has been demonstrated to be phosphorylated by hexokinase but not further metabolized. The rate of fructose incorporation into glycogen was 59% lower ($P < 0.01$) when muscle strips were co-incubated with fructose (1 mM) and 2-deoxyglucose (30 mM) (37.6 ± 8.3 compared with 91.0 ± 9.2 nmol/h per g for muscles incubated in the presence and absence of 2-deoxyglucose respectively). Fructose oxidation was not altered by the presence of 2-deoxyglucose (7.2 ± 0.9 and 8.6 ± 0.5 nmol/h per g in the presence and absence of 30 mM 2-deoxyglucose respectively).

Contributions of fructose to hexose metabolism

In the presence of physiological concentrations (5.0 mM) of glucose and fructose (at 0.1 or 0.5 mM), the contribution of fructose to hexose (glucose + fructose) incorporation into glycogen amounted to 9% (0.1 mM fructose) or 33% (0.5 mM fructose) (Table 4). Under insulin-stimulated conditions, using a concentration of the hormone that maximally stimulates GLUT4-mediated glucose transport in human skeletal muscle [21], the contribution of fructose to hexose incorporation into glycogen decreased to 3% (0.1 mM fructose) or 13% (0.5 mM fructose) (Table 4). The decreased contribution of fructose to hexose metabolism in the insulin-stimulated state is supported by our finding that fructose uptake is not regulated by insulin (Table 1), whereas in skeletal muscle, glucose uptake and GLUT4 translocation to the plasma membrane is markedly increased by insulin stimulation [22,23]. The contribution of fructose to hexose (glucose + fructose) oxidation in the basal state amounted to 7 and 32% for muscle strips co-incubated with 5 mM glucose and 0.1 mM or 0.5 mM fructose respectively (Table 4). Under insulin-stimulated conditions, the contribution of fructose to hexose (glucose + fructose) oxidation was reduced to 2 and 15% in the presence of 5 mM glucose and 0.1 mM or 0.5 mM fructose respectively (Table 4).

DISCUSSION

Using an *in vitro* technique to study hexose uptake and metabolism in isolated human skeletal muscle, we provide the first direct evidence that skeletal muscle has the distinct capacity to utilize physiological concentrations of fructose as a metabolic substrate. Although the importance of fructose as a metabolic substrate for human skeletal muscle is not fully understood, circulating levels of this sugar in humans have been estimated to be of the order of 0–1.0 mM [24,25]. Here we demonstrate that, under non-insulin-stimulated conditions, fructose could account for between 10 and 30% of total glycogen formation in the presence of physiological concentrations of glucose and fructose. Under insulin-stimulated conditions (1000 μ-units/ml), the contribution of physiological concentrations of fructose to glycogen formation decreases to 3–13%, mainly because of the pronounced stimulatory effect of insulin on uptake and metabolism of glucose but not fructose.

When fructose is infused intravenously during and after exercise in man, its uptake is enhanced in the exercising muscle, whereas glucose uptake remains unchanged [26]. Consequently, fructose uptake has been proposed to be mediated by a transport system that differs from that described for glucose [24]. Nevertheless, the precise mechanism by which fructose is transported into human skeletal muscle has not been delineated. In contrast with that for fructose, the transport system for glucose in skeletal muscle is more clearly defined, and is considered to be mediated predominantly by GLUT4 [23].

Cytochalasin B, a well-known inhibitor of GLUT1- and GLUT4-mediated hexose transport [9,21], completely inhibited insulin-stimulated glucose incorporation into glycogen and glucose oxidation (Table 2). In contrast with the marked inhibition of glucose metabolism by cytochalasin B, neither oxidation nor non-oxidative fructose metabolism was inhibited under basal conditions (Table 1). Thus, in human skeletal muscle, the glucose-transport system is dependent on the cytochalasin B-inhibitable GLUT1- and/or GLUT4-mediated glucose transporters, whereas the fructose-transport system appears to be mediated by a system that is independent of GLUT1 and GLUT4.

In addition to GLUT4, GLUT5 protein was readily detectable by Western-blot analysis of crude membranes of human vastus lateralis skeletal-muscle biopsies. Both earlier fractionation studies [10] and immunofluorescence studies [9] of human skeletal muscle have revealed that the high-affinity fructose transporter, GLUT5, is localized to the plasma membrane in these tissues, and does not undergo further recruitment to the plasma membrane on insulin stimulation. When mRNA for human GLUT5 is transfected into *Xenopus* oocytes, the expressed protein mediates the transport of D-fructose, but not D-galactose, methyl α-glucopyranoside or 3-*O*-methylglucose, suggesting that it is a high-affinity fructose transporter [11]. On the basis of the present

finding that fructose metabolism is not affected by cytochalasin B, GLUT5 is a likely candidate for the mediation of fructose transport in human skeletal muscle. GLUT5 has been readily detected by Western-blot analysis of the vastus lateralis muscle [10], but, in order to confirm fully the hypothesis that it is a specific fructose transporter, fructose transport must be measured in the presence of a specific inhibitor of this protein. At present, this hypothesis cannot be conclusively tested, as there is no known specific inhibitor of GLUT5.

Gluconeogenesis is believed to occur in skeletal muscle as the result of a marked increase in the extracellular lactate as found during heavy intermittent exercise [27]. Consequently our calculated percentage for *in vitro* fructose incorporation into glycogen should provide a fairly accurate estimate of glycogen metabolism in skeletal muscle. Thus, even in the presence of postprandial concentrations of insulin and glucose, blood fructose levels can make an important contribution to skeletal-muscle glycogen formation. Of the three components of fructose metabolism assessed in skeletal muscle, the greatest fraction underwent lactate formation. In the presence of physiological concentrations of fructose or glucose, ~ 79 or ~ 85% respectively of the calculated total metabolism (oxidation, glycogen synthesis and lactate formation) could be accounted for by lactate production. Insulin decreased these contributions to ~ 72% for 0.5 mM fructose and ~ 68% for 5 mM glucose, where glycogen formation increased to ~ 25% of total metabolism in both cases. The relationship between the contribution of the three major metabolic pathways to total metabolism observed in the present study is compatible with that previously reported for isolated human skeletal muscle [28]: during incubation of isolated rectus abdominal skeletal-muscle strips, non-oxidative glycolysis accounted for 74%, glycogen formation for 24% and glucose oxidation for 2% of total metabolism.

The glucose analogue 2-deoxyglucose, which is phosphorylated by hexokinase but not further metabolized, displaced fructose incorporation into glycogen to the same extent as glucose. Interestingly, in the absence of insulin, comparable rates of hexose incorporation into glycogen were observed when experiments were carried out at physiological concentrations for each sugar (Tables 1 and 2). Our findings of a rapid uptake of fructose by skeletal muscle agrees with previous studies *in vivo* in man [5,6] and dogs [6] in which indirect comparisons of uptake rates for fructose and glucose were performed. Fructose uptake by peripheral tissues has been demonstrated to occur at rates as high as or higher than those reported for glucose [5,6]. Furthermore kinetic studies reveal that the fructose-transport system in isolated adipocytes displays a more than 2-fold higher maximum velocity than the glucose-transport system. At present it is not known whether or not the difference in the metabolic rate between the two hexoses is due to differences in transport-protein content, activity level or substrate affinity.

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Here we provide the first direct evidence for fructose uptake in human skeletal muscle, which is mediated via a transport system that does not appear to involve GLUT1 or GLUT4. Furthermore, the uptake of fructose in human skeletal muscle can significantly contribute to carbohydrate metabolism. In the light of the present finding of a direct utilization of fructose in human skeletal muscle, further studies are required to ascertain the role of GLUT5 in fructose transport in human skeletal muscle.

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